UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/812,716	03/30/2004	Choong-Chin Liew	4231/2055E	5359

29933 7590 11/14/2008
Edwards Angell Palmer & Dodge LLP
111 HUNTINGTON AVENUE
BOSTON, MA 02199

EXAMINER	
SWITZER, JULIET CAROLINE	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
11/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/812,716	LIEW, CHOONG-CHIN	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *38-42 and 44-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-10,12-15,17,19,20,25,26,28,30-32,37,54,55,64,65,67,68 and 71-78* is/are rejected.

7)☒ Claim(s) *34-36* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-5,7-10,12-15,17,19,20,25,26,28,30-32,34-42,44-52,54,55,64,65,67,68 and 71-78.

DETAILED ACTION

1. Applicant's election without traverse of Group I, further electing the gene DZIP1 in the reply filed on 3/26/07 is acknowledged.

2. Claims 1-5, 7-10, 12-15, 17, 19-20, 25-26, 28, 30-32, 34-36, and 54-72 are included within the elected invention and examined herein. Claims 34-36 are included with the elected invention because these are method claims which depend from claim 32. Their inclusion in group II in the restriction mailed 9/27/06 was in error.

3. Claims 38-42 and 44-52 are withdrawn from prosecution as being drawn to a non-elected invention. Claim 38 is withdrawn because it requires "two or more genes selected from the group of genes listed in table 3G," and the combination applicant elected is a single gene.

Claim Objections

4. Claims 34, 35, and 36 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim must depend from previous claims in the alternative. See MPEP § 608.01(n). Accordingly, the claims not been further treated on the merits.

5. Applicant traversed the objection stating that the claims only refer to one set of claims. This misses the point. The problem is that the claims do not refer to the previous claims in the alternative, referring, for example to both claim 30 and claim 2. Further, these multiply dependent claims depend from claim 30 which is itself also multiply dependent. Thus, the claims are problematic for at least these two reasons. Applicant is reminded that 37 CFR 1.75(c) states, in part, "Any dependent claim which refers to more than one other claim ("multiple

dependent claim ") shall refer to such other claims in the alternative only. A multiple dependent claim shall not serve as a basis for any other multiple dependent claim."

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 2, 5, 7, 8, 9, 25, 26, 30, 31, 32, 37, 54, 55, are rejected under 35 U.S.C. 103(a) as being unpatentable over Page et al. (Biochemical and Biophysical Research Communications, 232, 49-53, 1997) in view of Sharma et al (WO 98/49342, as cited in IDS).

Page et al. teach a method for detecting differential expression of genes at different stages in the development of the development of diabetes in model rats. Page et al. use oligonucleotides of predetermined sequence in a slot blot to examine differential expression between kidneys of 6 week old and 26 week old GK rats, which are well characterized model of non-insulin dependent diabetes mellitus (i.e. Type II diabetes). The method of Page et al. includes using an oligonucleotide of predetermined sequence (the bands of interest were sequenced p. 50) in slot blot screening to detect and quantify differential expression of eight different genes that were identified as being differentially expressed between 26 week old GK rats and 6 week old control subjects (p. 50-51 and Table 1).

The slot blot used by Page et al. is an array (see Figure 1) which contains cDNA fragments (p. 50).

Page et al. do not teach a method wherein the total RNA in a blood sample is tested, nor does Page et al. teach a method wherein the subjects are human.

Sharma et al. teach that from the very early stages of diseases the whole organism response to the changed condition (p. 10, 4th full ¶). In light of this, Sharma et al. teach a method for identifying a marker useful for diagnosing a disease comprising the steps of detecting the presence of RNA in an unfractionated sample of whole blood from each of one or more subjects having said disease and quantifying a level of said RNA in said sample. Namely, Sharma et al. teach the preparation of gene transcript patterns beginning with extraction of mRNA from tissues, cells or body parts of an individual or organism which has a disease or condition (p. 7, final ¶, p. 12, 1st ¶), and particularly teach the isolation of total blood mRNA from whole blood samples (p. 35, section 5.1.1) (Total blood RNA meets the limitations of all of the different types of blood RNA recited in the claims.).

Sharma et al. teach quantifying the level of expression and determining a difference between the quantified level in the sample from the diseased subject and a similarly quantified level of genes of control RNA from an unfractionated sample of whole blood from each of one or more first control subjects (p. 5, step (d); p. 15, first full ¶; p. 18, step (f); p. 11, final ¶). Sharma et al. teach that these methods are carried out by producing amplification products from RNA extracted from an unfractionated sample of whole blood (p. 18 and p. 35, Example 5).

Sharma et al. teach that the invention can detect diseases years before other subjective or objective symptoms may appear (p. 11, third full ¶).

Sharma et al. teach that diagnostic patterns can be provided that include markers of disease progression (p. 7, first ¶).

Sharma et al. teach the detection of many genes, including second, third, etc. (p. 16) genes and teach the sampling of more than one diseased and/or control subject to determine quantified levels of expressed markers (p. 21, first full ¶).

Sharma et al. teach detecting RNA by detecting cDNA derived from RNA (p. 18, steps (c) and (d), for example).

Sharma et al. teach quantifying the level of control RNA in said sample (p. 5, step (d); p. 15, first full ¶; p. 18, step (f); p. 11, final ¶). Sharma et al. teach isolating the control RNA into bands on an electrophoresis gel for quantification (p. 13).

Sharma et al. teach isolating RNA via extraction prior to the detection step (p. 12).

Sharma et al. teach that the subjects include human subjects (p. 7, 2nd full ¶).

Sharma et al. teach that control subjects should be free of disease (p. 9, first full ¶).

Sharma et al. teach that their methods will result in the selection of between 2 and 1000 probe species for isolation, and that these probes reflect genes which have altered expression in the diseases or conditions in question, or particular stages thereof (p. 16, beginning at line 8).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Page et al. so as to have additionally tested the blood of the subjects having diabetes control samples and in particular to have completed this testing on total blood RNA. One would have been so motivated by the express teachings of Sharma et al. that disease exerts a global effect on individuals and that this effect can be measured by gene expression in the blood. The identification of markers for disease in the blood suggests a potential minimally invasive method to detect diabetes, namely type I diabetes. Furthermore, regarding the claims which require the use of human test subjects,

it would have been prima facie obvious to one of ordinary skill in the art to have modified the methods taught by Page et al. in view of Sharma et al. so as to have applied the methods for finding markers and measuring differential expression to human subjects, since, ultimately, diabetes is a disease that often affects humans. Page et al. teach that diabetic nephropathy is the major cause of end-stage renal failure in the Western world and that ultimately their goal is to identify genes that display transcriptional changes during the development of diabetes (p. 49).

Regarding the requirement that the subject genes are genes that are expressed in blood and non-blood tissue of a subject not having said disease, this is considered to be an inherent property of at least some of the genes that would be detected by the methods taught by Page et al. in view of Sharma et al. This is also true of the limitation which requires that the markers are predominately expressed in non-lymphoid tissues and that the markers correspond to non-immune response genes.

8. Claims 3, 4, 5, 7, 8, 9, 25, 26, 30, 31, 32, 37, 54, and 55, are rejected under 35 U.S.C. 103(a) as being unpatentable over Page et al. in view of Sharma et al. (WO 98/49342, as cited in IDS) and further in view of either Ralph et al. (WO 98/24953) or Ralph et al. (US 6190857).

9. Claims 5, 7, 8, 9, 25, 26, 30, 31, 32, 37, 54, and 55, are included in this rejection to address their alternative dependency from one of claims 3 or 4.

The teachings of Page et al. in view of Sharma et al. are previously discussed in this office action.

Ralph et al. carry out differential display method that is very similar to the one taught by Sharma et al. to identify markers of disease in blood and then confirm the differential expression

using RT-PCR. Namely, Ralph et al. teach that responses secondary to disease states may be reflected in changing patterns of leukocyte mRNA levels that correlate with the presence of the disease state (Col. 5, lines 27-33). Throughout, Ralph et al. teach a method of identifying differentially expressed markers using RNA fingerprinting, and the techniques used by Ralph et al. include amplification of mRNA using random primers and identifying differentially expressed molecules using gel electrophoresis. Ralph et al. further explicitly teach that "frequently mRNAs identified by RNA fingerprinting or differential display as being differentially regulated turn out not to be so when examined by independent means. It is, therefore, critical that the differential expression of all mRNAs identified by RNA fingerprinting be confirmed as such by an independent methodology (paragraph bridging Col. 98-100)."

Ralph et al. exemplify this confirmation method in Example 5.6.2, beginning in column 98. Ralph et al. teach the use of RT-PCR to identify two or more markers useful for diagnosing a disease exemplifying this method for the detection of two transcripts referred to by Ralph et al. as UC331 and UC332, these sequences are RNA encoded by each of two genes (Example 5.6.2 and following, Col. 98). The primers used by Ralph et al. include primers that are 15-25 nucleotides in length.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Page et al. in view of Sharma et al. so as to have included the RT-PCR step using oligonucleotides of predetermined sequence as taught by Ralph et al. so as to have provided a means to confirm the differential expression of the identified markers.

10. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sreekumar et al. (Diabetes, Vol. 51, June 2002, pages 1913-1920) in view of Affymetrix GeneChip Human Genome U133 Set information sheet (2001, Afymetrix, Inc) and also in view of Sharma et al.

The claims rejected in this section do not have the benefit of priority to the 10/268730 filing. The first mention of DZIP1 as being a gene differentially expressed in diabetes patients versus normal controls is the 10/601,518 application in which DZIP1 is disclosed on page 736 identified as spot number 10110. Therefore, claims which mention DZIP1 receive benefit only to the 10/20/03 filing date.

Sreekumar et al. teach a method which comprises steps of using an oligonucleotide of predetermined sequence to detect the presence of RNA in samples of RNA encoded by genes, quantifying the expression, determining the difference between the quantified level and a quantified level of a control RNA from control subjects. In particular, Sreekumar et al. measured the gene transcript alterations in patients with type 2 diabetes 2 weeks after withdrawing their treatment and then again after 10 days of insulin treatment, and then compared with control subjects with no family history of diabetes (p. 1913 and throughout). Sreekumar et al. teach using Hu6800 arrays which contain probes for approximately 6800 human genes (p. 1914).

Sreekumar et al. do not teach a method wherein differential expression of DZIP1 was tested, nor do they teach a method in which expression of genes in RNA of blood samples which have not been fractionated into cell types was tested.

Affymetrix provides the human genome U133 microarray set which is for monitoring the relative mRNA abundance of approximately 31,000 human genes. This array inherently includes probes to the human DZIP1 gene.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method taught by Sreekumar et al. so as to have used the U133 microarray set taught by Affymetrix for the expected benefit of assaying more human genes in the assay.

These together do not teach wherein the blood sample is genes in RNA of blood samples which have not been fractionated into cell types was tested.

Sharma et al. teach that from the very early stages of diseases the whole organism response to the changed condition (p. 10, 4th full ¶). In light of this, Sharma et al. teach a method for identifying a marker useful for diagnosing a disease comprising the steps of detecting the presence of RNA in an unfractionated sample of whole blood from each of one or more subjects having said disease and quantifying a level of said RNA in said sample. Namely, Sharma et al. teach the preparation of gene transcript patterns beginning with extraction of mRNA from tissues, cells or body parts of an individual or organism which has a disease or condition (p. 7, final ¶, p. 12, 1st ¶), and particularly teach the isolation of total blood mRNA from whole blood samples (p. 35, section 5.1.1) (Total blood RNA meets the limitations of all of the different types of blood RNA recited in the claims.).

Sharma et al. teach quantifying the level of expression and determining a difference between the quantified level in the sample from the diseased subject and a similarly quantified level of genes of control RNA from an unfractionated sample of whole blood from each of one or more first control subjects (p. 5, step (d); p. 15, first full ¶; p. 18, step (f); p. 11, final ¶). Sharma et al. teach that these methods are carried out by producing amplification products from RNA extracted from an unfractionated sample of whole blood (p. 18 and p. 35, Example 5).

Sharma et al. teach that the invention can detect diseases years before other subjective or objective symptoms may appear (p. 11, third full ¶).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Sreekumar et al. in view of Affymetrix so as to have additionally tested the blood of the subjects having diabetes and control samples and in particular to have completed this testing on total blood RNA. One would have been so motivated by the express teachings of Sharma et al. that disease exerts a global effect on individuals and that this effect can be measured by gene expression in the blood. The identification of markers for disease in the blood suggests a potential minimally invasive method to detect diabetes. The practice of this combined method necessarily would have resulted in determining a difference in expression in DZIP1 between healthy control and test samples, and so, in view of these teachings, the claimed invention is prima facie obvious.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 12-15, 17, 19-20, 25-26, 28, 30-32, 37, 64-65, 67-68, and 71-78 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention

There are a variety of independent claims included in this rejection.

Claims 12-15 and those that depend from these claims are drawn to a method for detecting a difference in gene expression of each of a gene or two or more genes in a human test subject suspected of having diabetes versus human control subjects. For each of a collection of a gene or two or more genes the claims require using an oligonucleotide of predetermined sequence or a primer specific only for said gene to quantify the presence of the RNA in a test sample and blood samples from the human test subject and determining a statistically significant difference where $p<0.05$ between the levels in the test versus control samples. The claims vary among themselves with regard to how the claim describes the test RNA sample, the number of genes required for detection, and the limitations regarding the means for detection. In some cases, though, the claims specifically require that the detected gene is a gene expressed in blood and in a non-blood tissue of a subject who is not a test subject. Thus, the claims require the knowledge of a relationship between the expression of two more genes that are expressed in blood and non-blood tissue of a subject and an indication of diabetes.

Claims 64-65, 67-68, and 71-72 are drawn to a method identifying a human test subject as being a candidate for having Type II diabetes. The claims all include a step of determining the level RNA encoded by a DZIP1 gene in a blood sample obtained from said human and comparing the level with the level of control RNA encoded by said gene in RNA of blood samples from control subjects, and wherein said comparison is indicative of diabetes in said human test subject. Thus, the independent claim, as written, states that a comparison of a human test subject DZIP1 RNA level in a blood sample to a control identifies the test subject as a candidate for having Type II diabetes and "is indicative of diabetes in said human test subject."

The nature of the invention requires the knowledge of a reliable association between comparing DZIP1 expression and the indication that the individual is a candidate for having type II diabetes and diabetes is present in a human. Further, the practice of the invention requires an understanding of how the presence of diabetes effects the level of DZIP1 expression in human blood.

In claims 73-78 the invention is drawn to a method a method for classifying DZIP1 gene expression in a human, and sets forth steps of quantifying a level of RNA encoded by a DZIP1 gene in a test subject, comparing that level to a level of RNA found in blood samples from control subjects having type II diabetes and also comparing it to control subjects who are healthy. The independent claim states that based on particular determinations, the classification of DZIP1 gene expression results either with that of said subjects having diabetes or with that of subjects who are healthy. The nature of the invention requires the knowledge of a reliable relationship between DZIP1 expression in blood and the presence of type II diabetes. Further, the practice of the invention requires an understanding of how the presence of type II diabetes effects the level of DZIP1 expression in human blood. The nature of the invention requires the knowledge of a reliable association between DZIP1 expression and the ability to classify a particular individual's expression with the expression of subjects having type II diabetes or not having type II diabetes, and further, the use of this method requires that there is an underlying assumption that this classification is meaningful. Reading the claims in light of the specification it is clear that applicant intends to use such a classification method in order to provide a tool that is used as part of a diagnostic process, and such a use requires the knowledge of a reliable association underlying the classification.

All of the claims require a step of comparing the level of RNA detected in a test subject to "a quantified level of control RNA encoded by said gene in blood samples of control subjects." To practice these claims, it is essential to know the quantified level of control RNA encoded by said gene in blood samples of control subjects.

Scope of the claims

Regarding claims 12-15 and those that depend from these claims:

The claims are broad in scope with regard to the fact that the test genes are entirely unidentified in the claims. However, they are limited in some cases such that they must be genes that are expressed in both blood and non-blood tissue of a subject and that the differential expression of these genes from a test to control subject must be "indicative of diabetes in said test subject."

Regarding claims 64-65, 67-68, and 71-72:

The claims are very broad in scope because they encompass that ANY level and direction of difference in gene expression is sufficient to classify the expression or to identify a candidate for disease. That is, the claims do not set forth that one level should be higher or lower than the other, and further do not set forth how much of a "difference" between two individuals would be necessary to draw the conclusions set forth in the claims.

Teachings in the Specification/Examples

The specification teaches the production of cDNA libraries from fetal heart, adult heart, liver, brain, prostate, and whole blood (example 1).

Example 2 teaches the random partial sequencing of cDNA clones from the blood cell library, and categorizing of the genes into cellular functions.

Example 3 teaches screening of cDNA probes from transcripts of non-blood tissues to identify transcripts that were expressed only in blood.

Example 4 teaches RNA extracted from human tissue was subjected to RT-PCR for amplification of cardiac beta-myosin heavy chain gene (βMyHC), amyloid precursor protein (APP), and adenomatous polyposis-coli protein (APC) gene. Example 5 teaches that these three genes, which were previously thought to have tissue specific expression were detected in whole blood samples.

Example 6 teaches the detection of insulin expression in a drop of blood of 4 normal subjects and it was found that the insulin expression in the blood of normal subjects is influenced by fasting and non-fasting states of normal healthy subjects (Fig. 2). No statistical analysis is provided for this result. The example further teaches analysis of a drop of blood from a single healthy person, a person having type II diabetes, and a person having asymptomatic diabetes, and it is taught that the insulin gene is expressed differently among these subjects (Fig. 3). The specification further teaches that the atrial natriuretic factor gene (ANF) was observed to be expressed in the blood of patients with heart failure and is significantly higher in the blood of patients with heart failure as compared to the blood of a normal control patient (¶57). No data is given to support this statement, for example it is not taught what difference is necessary between patient and control in order for the difference to be indicative of disease. The specification teaches differential expression of ZFP amongst normal, diabetic and asymptomatic subjects (Fig 4), but does not associate this difference with the indication of any disease. Example 6 further

demonstrates that the housekeeping gene glyceraldehydes dehydrogenase is not differentially expressed in the blood of disease vs. normal subjects.

The specification teaches in Example 7, that nearly 95% of the clones identified in a human blood cell library are identical between blood and other tissue samples (¶62). The specification teaches that of 20,000 seqeunced EST's from blood cell cDNA library, 17.6% appeared to be novel against GenBank, and others were known. Table 2 provides a list of 1800 genes that were previously thought to be "tissue specific" whose expression was detected in whole blood (beginning on p. 6).

Regarding diabetes in particular, the specification also provides example 16 wherein gene expression profiles of blood samples from individuals having type 2 diabetes were compared with normal individuals, that is patients who presented without type 2 diabetes, but may have presented with other medical conditions and may be under various treatment regimes (p. 73, lines 19-20). The example specifically teaches that "diabetes" includes both "'type 1 diabetes' (insulin-dependent diabetes (IDDM)) and 'type 2 diabetes' (insulin-independent diabetes (NIDDM)," however, only patients having type 2 diabetes were tested as compared to normal patients (specification page 72). Example 16 teaches that 915 different genes were differentially expressed with a p value of <0.05 as between the type 2 diabetes patients and the combination of normal and non type 2 diabetes individuals. The table 3G provides a list of these genes (Example 16). DZIP1 is among the genes.

The tables list genes that were differentially expressed, but does not provide any further information regarding the level of expression. For example, the tables do not teach if the expression was higher or lower in diabetes patients versus controls.

The specification does not provide any guidance as to the level of "difference" that is sufficient (1 fold, 2 fold, etc) to result in a conclusion that type 2 diabetes or diabetes in general is detected, nor does the specification provide any guidance as to the direction of the difference (higher or lower expression) that is expected to be observed for any single pairing of samples. The claims suggest that detecting and comparing expression of DZIP1 alone is sufficient to indicate the presence of diabetes (that is to detect diabetes). The plain language of the claims suggests that any comparison between a test subject and control subjects, even as few as two control subjects, is sufficient to conclude that all diabetes is detected.

The specification fails to provide information about an essential aspect of the invention, namely, the nature of the difference in expression that was observed between type 2 diabetes patients and non-type 2 diabetes patients. Furthermore, though the specification teaches that this gene is differentially expressed in type 2 diabetes patients versus non-type 2 diabetes patients, the specification teaches this is true for hundreds of genes. There is no guidance or analysis of data in the specification to suggest that this gene in particular is sufficient to conclude that diabetes is present in a sample, as is instantly claimed. This information is essential to understanding and practicing the claimed invention because it is critical to knowing how to interpret a particular comparison result.

The concerns raised with regard to DZIP1 apply equally to each of the 915 genes disclosed in instant table 3G. That is, for the same reasons, the data in the specification is not sufficient to appraise one of skill in the art as to how to determine which of these molecules could be used to practice an invention were a difference in expression between a test subject and control subjects is "indicative of diabetes."

State of the Prior Art and Level of Unpredictability

At the time the invention was made, it was known that expressed genes in whole blood could be indicative of some diseases, see for example the teachings of Sharma et al. and Ralph et al. cited in this office action. However, establishing that a particular marker is differentially expressed in a manner reliable enough to use the marker to indicate the presence of disease in a test subject is a highly unpredictable endeavor.

The expression of genes in example 16 was tested by hybridization of samples to a microarray that contains genetic information for tens of thousands of genes. This technology area is highly unpredictable, and as a result significant guidance is required to practice inventions using this type of data. Lee (Clinical Chemistry, 47:8, 1350-1352 (2001)) teaches that despite the technical accuracy of individual observations on an array, these data "are much more prone to numerous false-positive findings fundamentally because of (a) an extremely large number of observations and (b) a very wide dynamic range of gene expression values obtained from gene chip experiments." In view of these unpredictable aspects of applying such data, Lee teaches that replication is necessary to begin to screen out false positive results. There is no replication in the instant specification.

Furthermore, there is no analysis of all possible diseases or phenotypes to determine if the gene expression difference observed in the instant application is specific to diabetes such that any difference between a test patient and blood samples from control subjects is sufficient to conclude diabetes is present. Kaizer et al. tested gene expression in the blood of children with diabetes and compared expression profiles among groups of patients having type 1 and type 2

diabetes and controls using microarray analysis (Journal of Endocrinol. Metab, September 2007, 92(9): 3705-3711). They found that type 1 and type 2 diabetes have some genes which are differentially expressed relative to healthy controls in common, and some which are different. Without proper testing, however, it is impossible to predict which genes fall into which category. Further, Takamura et al. used microarray analysis to identify differentially expressed genes between patients having type 2 diabetes and healthy controls. The caution that further studies are necessary to "clarify the effects of age, gender, type of diabetes, complications, treatment regimens for diabetes, other pharmacological treatments for hypertension and hypertension, etc." before potential biomarkers identified by such a study could be used for diagnostics (Takamura et al. Biochemical and Biophysical Research Communications, 361 (2007) 379-384, especially page 384). Each of these steps would equally be required before one could use any of the markers provided in table 3G, and the outcome of such further analysis is highly unpredictable. So first, even if one carried out the claimed analysis on a test subject, and if one observed a level of expression, it is highly unpredictable how would one begin to know if that level of expression indicated type 1 diabetes, type 2 diabetes, both, one but not the other, something in between or even some other condition or disorder for which the expression profile has not yet been determined. Furthermore, although DZIP1 was not observed to be differentially expressed in any of the other examples in this specification, it is unknown and unpredictable whether it would be expressed in the blood of patients having other diseases or any other diseases which were not tested in the instant specification or diseases which were tested in the instant specification but in a different population of test subjects, and whether this expression would be different from levels of expression in healthy controls. A method for detection which relies on a comparison between

expression in the blood of a test subject and control subjects requires the knowledge of this information in order to reliably suggest diabetes is present or classify an individual's expression with diabetes, as set forth in the claims. The instant specification has not established that all difference, no matter the magnitude nor the direction, relative to any control subjects or even relative to a healthy control subject is indicative of diabetes in general or type II diabetes. It is not known under what circumstances the result observed in the instantly examined control and test populations would be repeatable, as the results have not been validated. But even if one were to obtain the same result, it would be unknown because applicant did not disclose the magnitude of difference in expression between coronary artery disease patients or controls, nor did applicant disclose the direction of variation. All of these inquiries are particularly important in this case since the specification is silent as to which differential expression observations would be sufficient to detect the presence of coronary artery disease.

Further, neither the specification nor the claims, for any individual gene, let alone two genes, or for all genes in general, set forth a threshold of difference between one individual and one or more control individuals that would be sufficient to conclude that the difference in gene expression between a healthy individual and any control individual is "indicative of disease."

Because the claims encompass any level of altered gene expression, it is relevant to point out that the art of Cheung et al (2003) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) (p.422, last paragraph; Fig 1). The data indicates that, for example, expression of ACTG2 in 35 individuals varied by a factor of 17; and

that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3). It is thus unpredictable as to whether or not any level of altered gene expression is indicative of a diabetes or the absence of diabetes.

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the post-filing art of Wu (2001). Wu teaches that gene expression data, such as microarray data, must be interpreted in the context of other biological knowledge, involving various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (p.63 - Discussion). The art of Newton et al (2001) further teaches the difficulty in applying gene expression results. Newton et al. teaches that a basic statistical problem is determining when the measured differential expression is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation (p.38, third full paragraph). There is no replication of data in the instant specification.

Quantity of Experimentation

The instant specification does not provide enabling support for the practice of a single embodiment within the claimed inventions. In particular, the specification does not provide adequate guidance to appraise one of ordinary skill in the art as to what levels of DZIP1 gene expression must be observed to successfully conclude that even type 2 diabetes is present. Further, although the specification teaches there are differences in DZIP1 levels in a type 2

diabetes population versus a control patient population, the specification is silent as to the nature of the "difference" in magnitude or direction. Thus, given the lack of teaching in the specification and the highly unpredictable nature of the technology, an extensive amount of work would be required to practice the claimed invention.

In order to practice the claimed invention, one would have to undertake an extensive amount of experimentation in a highly unpredictable technology area. One would begin by trying to reproduce the results observed in the instant specification to determine if there is a relative upregulation or downregulation of DZIP1 (or any of the other 914 genes given in Table 3G) in diabetes patients versus healthy control patients, as the specification does not even provide this minimal guidance. Without this knowledge one would not even begin to know how to interpret any results obtained in practicing the claimed methods. For example, consider the comparison of a test result and a control population of healthy individuals. How different from the average level of expression of healthy individuals would the test result have to be to indicate diabetes? Would any difference, up or down regulation be indicative of type 2 diabetes or type 1 diabetes or both? Or could one indicate diabetes and one a different undisclosed disease? Is DZIP1 expressed in the blood of individuals with a disease other than type 2 diabetes? Is this expression also diagnostic of other type 1 diabetes or asymptomatic diabetes or other autoimmune diseases or other disorders entirely unrelated to diabetes? In order to reliably use a method for detecting diabetes, one would first have to answer at least these questions. One would also, however, have to carry out this testing for validation, for it is possible that the result observed in the instant specification is intrinsic to the cohort of patients evaluated in applicant's

study. Further, one would have to undertake experimentation to determine difference thresholds required to determine that a patient has or does not have a disease.

As discussed, this art area is highly unpredictable.

Conclusion

The claims include methods which encompass the detection in blood of the expression of DZIP1 in a test subject and comparing this expression to control subjects, wherein the comparison itself "is indicative of diabetes." The claims also include methods wherein the subject gene or genes are entirely undefined, that is sufficiently broad so as to encompass any possible gene whose differential expression in the blood might be indicative of any type of diabetes. The identification of gene differential expression/disease indication relationships is a highly unpredictable endeavor, requiring extensive experimentation. The specification provides minimal guidance. In light of the factors discussed, therefore, it is concluded that it would require undue experimentation to practice the claimed invention.

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference

claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1. Claims 1-5, 7-9, 12-15, 19-20, 25-26, 28, 30-32, 37, 54, and 55, are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 17, 19-21, 23-24, 28-29, 31, 33-34, 38, 41, 43, 49, 56, 59, 61, 62, and 63 are of copending Application No. 10/601518. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claims are either obvious or anticipated in view of the claims of the copending application. In particular, the claims of the copending application recite methods for identifying markers and detecting differential expression among test individuals relative to control individuals. Claim 59 of the copending application specifically recites that the disease is diabetes. Therefore, at the time the invention was made, it would have been prima facie obvious to one of ordinary skill in the art to have practiced any of the methods provided in the copending application, wherein the disease is diabetes, following the specific guidance given in the claims of the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. Claims 1-5, 7-9, 12-15, 19-20, 25-26, 28, 30-32, 37, 54, and 55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 67-93 of copending Application No. 10/268730 in view of Page et al. The copending claims recite methods for determining differential expression of genes in disease, the methods are generic to the instantly claimed methods, but very similar in structure. The copending claims recite a method wherein the disease is diabetes, see claim 79.

15. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by the copending application so as to have practiced them relative to the study of diabetes. One would have been motivated to screen for genes that are differentially expressed in the blood of humans in order to provide a means for detecting diabetes.

This is a provisional obviousness-type double patenting rejection.

Response to Remarks

Applicant's remarks which are not otherwise addressed are addressed here in the order in which they were presented in the response.

Applicant traverses the rejection for lack of enablement. On page 25 of the response applicant disagrees with the examiner's statement that "the test genes are entirely unidentified" because the test genes are identified throughout the specification. This portion of the rejection intends to refer to the fact that the claims are generic in nature- the test genes are entirely

unidentified in the claims. The rejection acknowledges and discusses the genes which are disclosed throughout the specification. Further, while the specification provides 915 genes differentially expressed with a p value of <0.05, the specification is silent as to which of these are genes that are expressed in blood and non-blood tissues of healthy individuals, as required by some of the claims at issue.

Applicant disagrees with the discussion about comparison to as few as two controls and notes that the amended claims include a limitation that the difference must be statistically significant where $p<0.05$. This portion of the rejection is withdrawn in view of the amendment to the claims.

Applicant states that a reliable association between an indication of diabetes and the expression of two or more genes that are expressed in a blood and non-blood tissue of a subject is present in the specification, referring to DZIP1 as an example (p. 26-27 of remarks). However, as noted in the rejection, the disclosure relative to DZIP1 and to all of the genes in Table 3G is incomplete since they do not disclose the magnitude or direction of the difference in expression of DZIP1 observed in the experiments. The results are not validated in a second population. Applicant disclosed that a difference in expression was identified but failed to disclose the nature of the difference. All of the claims require comparing the level of expression with quantified levels from control subjects, but the specification provides no guidance at all as to what these quantified levels are. Based on the teachings of the specification, one would have to begin again applicant's experimentation. Since the nature of the control values are entirely unpredictable based on applicant's disclosure, one would have to determine these values, then validate them. This is not simply routine experimentation since the technology of establishing a

relationship between gene expression and a phenotype is an empirical and unpredictable technology. This is a critical feature of the claimed invention, and a significant lack of disclosure.

Applicant points out that for insulin and zinc finger protein the magnitude and direction of the change are given in Figure 5. However, these experiments are clearly preliminary in nature- only a single diabetic subject was tested relative to three healthy subjects. No statistical analysis is provided. Further, these two examples, even if robust, validated data were provided would not be sufficient to enable the full scope of the claims as they do not bear a reasonable correlation to the full scope of the claim which encompasses using any possible gene that meets the functional limitations. They are not elected embodiments for the specific genes to be considered (DZIP1 was elected). So, further discussion of only these two genes is not provided.

Applicant disagrees with the examiner's statement that no replicate data is found in the instant specification, pointing to the fact that multiple tested subjects constitutes a replication. It is agreed that these are replicates within the single experiment which was analyzed. However, the total experimentation was not replicated for the purposes of validation.

Applicant points out that the claims are not meant to function as a method which would necessarily be a test to be relied on for the detection of diabetes to the exclusion of other diseases (p. 28). Applicant points out that in the Metabolite patent the assay for elevated homocystein levels could signal a risk of heart disease, while the claims of the Metabolite patent set forth that the elevated homocysteine in the body fluid is correlated with a deficiency of cobalamin or folate. Applicant points out that this issue was never raised in litigation regarding the validity of this patent. This is not a persuasive argument. The absence of the argument does not mean that

it could not have been a valid point. Further, in this case, the issue of ambiguity of classification is one of many different factors considered to arrive at the conclusion of lack of enablement. The issue is present and remains present in the context of many other complicated and unpredictable issues, as discussed in the rejection.

Applicant reminds the Office that a considerable amount of experimentation is permissible to practice the claimed invention if it is merely routine. However, having considered all of the factors set forth in the rejection, the examiner maintains that the quantity of experimentation would not be routine. Applicant cites Slonim who states that the most basic question one can ask is which genes expression levels change significantly, and Applicant points out that the identity of the differentially expressed genes was provided in table 3G. It is a misrepresentation of this reference to suggest that Slonim suggests that methods of classification of individuals can and should be practiced without knowledge of the nature of the expression of a target gene. While Slonim does state that the most basic question is which genes expression levels changes, she also discusses at length that this itself is a complicated question. Here, the instant claims are drawn to making a classification of an individual based on the expression of a single gene. All of the methods for classification discussed by Slonim rely on inputted data regarding the exact nature of the change in expression. Slonim teaches that often classification of the a training set may be perfect, but subsequent attempts to classify new test data fail dismally, pointing out that sample prediction from array data is particularly challenging (p. 506).

The instant specification fails to provide a critical piece of information with regard to understanding the relationship between the expression of the genes in the table and type II diabetes, and the expression of DZIP1 in particular. The specification invites one of skill in the

art to undertake experimentation to (a) determine the relationship between type II diabetes and DZIP1 (or any other gene) expression and then to validate that relationship. There is a fundamental absence of information given in the specification. The claims all set forth comparing the test level to "a quantified level of RNA encoded by said gene in blood samples from control subjects…" but the specification does not provide this quantified level, or any quantified level. So, it is left to one of skill in the art to establish what is critical for the practice of the invention. While the specification may rely on the state of the prior art to help enable the invention, the specification may not rely on the state of prior art to supplement what is critical to the practice of the invention- in this case the quantified levels of control RNA encoded by the gene in the control subjects, no matter which type of control subjects.

The rejection for lack of enablement is maintained.

Applicant traverses the rejection under 103 beginning on page 31 of the remarks. Applicant summarizes some case law relevant to 103 and summarizes the claims at issue on pages 31-34 of the response.

It is noted that claims 12-15 and those claims that depend only from these have not been included in the 103 rejections in this office action. Their inclusion in the rejections in the previous office actions was inadvertent.

On page 35 applicant points out that Page et al. does not contemplate or consider the identification of useful diabetes-related markers directly from whole blood. This is a piecemeal analysis which does not consider the totality of the rejection. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re*

Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

This claim element is provided in the secondary reference, Sharma et al. Regarding Sharma, applicant states that Sharma does not at any point teach or suggest looking in whole blood for markers or differentially expressed genes of diabetes. Sharma is quite clear, however, in their teaching that from the time an individual becomes diseased the entire body reacts, and that they consider their invention to be applicable to a wide variety of diseases, as discussed in the rejection. Here, the claims are to methods of simply determining that differential expression exists- the method is a screening method. Applicant points out that Sharma does not exemplify detecting markers for a mammalian disease. Applicant is reminded that MPEP 2123 teaches that "A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments… Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments." Here, Sharma expressly suggests using their methods to find markers for a wide array of human diseases which have no common etiology or features. Sharma's disclosure is suggestive that their methods can be applied to virtually any disease or condition.

Applicant argues that Sharma's suggestion that any disease can be detected by examining its effects on gene expression in the blood, particularly in view of the Office action's admission that the pertinent art is highly unpredictable would hot have been enough to motivate the skilled artisan to take Page beyond its teachings to reach the present invention. It is important to note the difference between the claims rejected under 112 1st paragraph and the claims at issue here. The claims under 112 1st paragraph are diagnostic or indicative in nature. To practice them one

of skill in the art would have to know about particular differentially expressed genes and the nature of the differential expression. The claims rejected under 103, however, are drawn to methods for identifying markers- they are screening methods. While the identity of the particular markers required for detection or indication or classification of disease is highly unpredictable, it is submitted, that based on the teachings of the art it is predictable that such genes would exist. The claims rejected under 103 were not included in the rejections for lack of enablement because these claims are enabled by the specification and by the prior art. Here, it is predictable based on the teachings of the prior art that markers could be identified, it is unpredictable still, however, what the identity of those markers actually is. Furthermore, it is noted that the references would have been understood within the context of the prior art at the time the invention was made. As cited in the previous office action, at the time the invention was made, at least one differentially expressed marker in human diabetics was known. Wei et al. teach that insulin dependent diabetes mellitus is a kind of autoimmune disease, and furthermore teach that IL-6 is differentially expressed in the blood of patients having diabetes versus control patients. Thus, Wei et al. exemplify at least a single differentially expressed molecule is present in the blood of patients having diabetes relative to healthy patients. It is within this prior art setting that one skilled in the art would have been considering the references. Applicant's arguments that the teachings of Sharma et al. would not have been sufficient to motivate one skilled in the art to practice the invention because there was no reasonable expectation of success are not persuasive. Absolute predictability is not required in order to establish an expectation of success. The MPEP states, "Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable

expectation of success may support a conclusion of nonobviousness (2143.02)." Here, there is no evidence to support a showing of no reasonable expectation of success. Attorney argument cannot replace evidence on the record. The rejection under Page in view of Sharma is maintained.

Applicant further traverses the rejection under Page and Sharma, further in view of Ralph. Applicant summarizes Ralph portions of Ralph on page 39, first full paragraph, and then refers to the rejected claims. Applicant states that the methods require the use of sequence specific primers in order to obtain measurable amplification products "of target biomarker genes of interest," pointing to those genes listed in Table 3G as examples. It is noted that none of the claims rejected under this combination refer to table 3G, and so this is a feature not claimed. Applicant argues that the recited steps of the rejected claims are drawn to a different method than the teachings of Ralph. Applicant argues that the rejected claims are drawn to methods of detecting biomarker genes directly in whole blood samples to aid in the detection of disease, whereas Ralph relates to the identification and confirmation of the markers themselves. To the contrary, the claims rejected under the prior art are all drawn to "methods of identifying a marker" or "two or more markers" and appear to be directed in fact to the discovery of markers in whole blood samples. Applicant argues that the present invention is directed to the detection of disease biomarkers in RNA samples, rather than confirming or validating a biomarker that has already been identified. Applicant's claims are drawn using comprising language, and therefore can include steps where the marker is identified and then verified, as part of the larger identification step. Further, applicant's arguments are all drawn to intended use of the claimed

methods, and fail to point to any structural difference between the claimed method and the method made obvious by the references. The rejection is maintained.

Applicant traverses the rejection under Sreekamur, Affymetrix, and Sharma et al. Applicants agree that it would have been obvious to modify Sreekamur so as to have used the Affymetrix chip to look for differential expression of transcripts in skeletal muscle of diabetic patients and healthy control subjects. Applicant traverses, however, the office's position that it would have been further obvious to modify these to look for transcripts in blood. Applicant reiterates their position that Sharma et al. do not discuss diabetes nor do they exemplify assaying for markers for diabetes or any other human disease. These arguments have been previously addressed in this office action.

On page 42 applicant further points out that no art has been cited which teaches a difference in expression in DZIP1 between healthy control and test samples. However, it appears this is a result that would inherently have flowed out of the assay which is obvious in view of the cited teachings, as stated in the rejection. IT would have been obvious to have practiced the steps of the claimed method, including determining the level of expression in both sample types, and comparing them to determine if there is a difference, for every single gene on the Affymetrix array, including DZIP1. It is predictable that the method could have been carried out. Here the predictable result is a practicable method, as the substitutions are being made within the context of the method steps. The rejection is maintained.

The obvious type double patenting rejections are maintained.

Conclusion

16. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

17. Wei et al. (Chinese Medical Journal, Volume 106(12):893-897, 1993).

Wei et al. teach that insulin dependent diabetes mellitus is a kind of autoimmune disease, and furthermore teach that IL-6 is differentially expressed in the blood of patients having diabetes versus control patients. Thus, Wei et al. exemplify at least a single differentially expressed molecule is present in the blood of patients having diabetes relative to healthy patients.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Tuesday or Wednesday, from 9:00 AM until 4:30 PM, and Thursday afternoon from 12:30 PM until 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Juliet C. Switzer/
Primary Examiner
Art Unit 1634

November 15, 2008